Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-203-z Pembrolizumab

Stand: Oktober 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Pembrolizumab
[Behandlung des nicht resezierbaren oder metastasierten Urothelkarzinoms; Erstlinientherapie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Pembrolizumab (Urothelkarzinom): Beschluss vom 16. September 2021 • Atezolizumab (Urothelkarzinom): Beschluss vom 16. März 2018 und Änderungsbeschluss vom 2. August 2018; Beschluss vom 20. Juni 2019 und Änderungsbeschluss vom 6. April 2023 • Avelumab (Urothelkarzinom): Beschluss vom 19. August 2021 Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI (Off-Label-Use): • Carboplatin in Kombination mit Gemcitabin zur Behandlung von Patientinnen und Patienten mit inoperablem lokal fortgeschrittenem oder metastasiertem Urothelkarzinom, wenn eine Cisplatin-Therapie nicht infrage kommt (Beschluss vom 20. Mai 2021)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen	Siehe „systematische Literaturrecherche“

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Pembrolizumab
[Behandlung des nicht resezierbaren oder metastasierten Urothelkarzinoms; Erstlinientherapie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Therapie im Anwendungsgebiet gehören.	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab L01FF02 Keytruda	<u>Anwendungsgebiet laut positive Opinion:</u> KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.
Cisplatin L01XA01 Generisch	Cisplatin wird angewendet zur Behandlung des: • fortgeschrittenen oder metastasierten Harnblasenkarzinoms • […]
Doxorubicin L01DB01 Generisch	• Systemische Therapie des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms • […] Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Epirubicin	Bei intravesikaler Anwendung hat sich Epirubicin bei der Behandlung folgender Erkrankungen als wirksam erwiesen:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01DB03 Generisch	• papilläres Übergangszellkarzinom der Harnblase • Carcinoma in situ der Harnblase
Methotrexat L01BA01 Generisch	Methotrexat 25 mg/ml Injektionslösung wird angewendet bei: • Harnblasenkarzinomen - in Kombination mit anderen zytotoxischen Arzneimitteln • […]
Gemcitabin L01BC05 Generisch	• In Kombination mit Cisplatin zur Behandlung des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms.
Pembrolizumab L01FF02 Keytruda	Pembrolizumab ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren, angezeigt. […]
Atezolizumab L01FF05 Tecentriq	Atezolizumab als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC) • die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5 % aufweisen. • […]
Nivolumab L01FF01 Opdivo	Nivolumab ist in Kombination mit Cisplatin und Gemcitabin für die Erstlinientherapie des nicht resezierbaren oder metastasierten Urothelkarzinoms bei Erwachsenen indiziert.
Avelumab L01FF04 Bavencio	Als Monotherapie in der Erstlinien-Erhaltungstherapie bei erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Urothelkarzinom (urothelial carcinoma, UC) angewendet, die nach einer platinbasierten Chemotherapie progressionsfrei sind.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-203z (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. September 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CSS	Cancer-specific survival
CTX	Chemotherapie
EAU	European Association of Urology
ECRI	Emergency Care Research Institute
EMA	European Medicines Agency
EV	Enfortumab vedotin
FDA	U.S. Food and Drug Administration
FGFR	Fibroblast growth factor receptor
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICIs	Checkpoint-Inhibitoren
IO	Immunotherapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
la/mUC	locally advanced ormetastatic urothelial cancer
LoE	Level of Evidence
mAb	monoclonal antibody
MIBC	Metastatic Bladder Cancer
MMAE	Monomethyl auristatin E
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death-Ligand 1
RNU	Radical nephroureterectomy
RR	Relatives Risiko
SJS	Steven-Johnson syndrome

TEN	Toxic epidermal necrolysis
TRIP	Turn Research into Practice Database
UC	Urothelial carcinoma
WHO	World Health Organization

1 Indikation

Erstlinienbehandlung des nicht resezierbaren oder metastasierenden Urothelkarzinoms bei Erwachsenen.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Urothelkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 08.12.2023 durchgeführt, die folgende am 14.08.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1561 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 9 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Maisch P et al., 2023 [4].

Immunotherapy for advanced or metastatic urothelial carcinoma

Fragestellung

To assess the effects of immune checkpoint inhibitors compared to chemotherapy as first- and second-line treatment of advanced or metastatic urothelial carcinoma.

Methodik

Population:

- participants with advanced or metastatic muscle invasive bladder cancer

Intervention/Komparator:

- immunotherapy vs. chemotherapy

Endpunkte:

Primary outcomes

- Time to death from any cause (time-to-event outcome)
- Health-related quality of life (continuous outcome)
- Adverse events grade 3 to 5 (dichotomous outcome)

Secondary outcomes

- Time to death from bladder cancer (time-to-event outcome)
- Time to disease progression (time-to-event outcome)
- Discontinuation due to adverse events (dichotomous outcome)

Recherche/Suchzeitraum:

- -08.2022
- Cochrane Library, MEDLINE, Embase etc.

Qualitätsbewertung der Studien:

- RoB 2

Ergebnisse

Anzahl eingeschlossener Studien:

Qualitative: 12

Quantitative: 5

Charakteristika der Population/Studien:

ADDITIONAL TABLES

Table 1. Baseline characteristics of included studies in first-line

Study name	Trial period (year to year)	Setting/ country	Intervention (I)/ comparator (C)	Description of participants	Duration of follow-up (median)	Age (years, median)	Gender (male/female (%))
Galsky 2020	2016 to 2018	Multicenter International, 35 countries	Intervention: atezolizumab	First-line, cisplatin-ineligible or -eligible, inoperable locally advanced or metastatic UC	11.8 months	67.0	280 (77%)/82 (23%)
			Comparator: gemcitabine + carboplatin or gemcitabine + cisplatin			67.0	298 (75%)/102 (26%)
			Comparator: atezolizumab + gemcitabine + carboplatin or gemcitabine + cisplatin			-[a]	-[a]
Powles 2020	2015 to 2017	Multicenter International, 23 countries	Intervention: durvalumab	First-line, inoperable locally advanced or metastatic UC	41.2 months	67.0	249 (72%)/97 (28%)
			Comparator: gemcitabine + carboplatin or gemcitabine + cisplatin				
			Comparator: durvalumab plus tremelilumab			68.0	274 (80%)/70 (20%)
						-[a]	-[a]
Powles 2021	2016 to 2018	Multicenter International, 21 countries	Intervention: pembrolizumab	First-line, inoperable locally advanced or metastatic UC	31.7 months	68.0	228 (74%)/79 (26%)
			Comparator: gemcitabine + carboplatin or gemcitabine + cisplatin				
			Comparator: pembrolizumab plus gemcitabine + carboplatin or gemcitabine + cisplatin			69.0	262 (74%)/90 (26%)
						-[a]	-[a]
Iacovelli 2022	2019 to 2021	Multicenter, 1 country	Intervention: avelumab	First-line, inoperable locally advanced or metastatic UC	9.0 months	75.0	NA
			Comparator: NA			NA	NA

NA: not available; UC: urothelial carcinoma.
[a]analysis of combination therapy not the topic of this review.

Qualität der Studien:

Risk of bias for analysis 1.1 Time to death from any cause

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Galsky 2020	✓	✗	✗	✓	✓	✗
Powles 2020	✓	~	✓	✓	✓	✓
Powles 2021	✓	~	✓	✓	✓	✓

Risk of bias for analysis 1.3 Adverse events grade 3 to 5

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Galsky 2020	✓	✗	✗	✗	✓	✗
Powles 2020	✓	~	✓	✗	✓	✗
Powles 2021	✓	~	✓	✗	✓	✗

Risk of bias for analysis 1.5 Discontinuation due to adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Galsky 2020	✓	✗	✗	✗	✓	✗
Powles 2020	✓	~	✓	✗	✓	✗
Powles 2021	✓	~	✓	✗	✓	✗

Studienergebnisse:

Immune checkpoint inhibitors versus any first-line chemotherapy

- Time to death from any cause
  - Immunotherapy probably has little to no effect on the risk of death from any cause in the first-line therapy setting (HR 0.97, 95% CI 0.87 to 1.07; I2 = 0%; 3 studies, 2068 participants; moderate certainty evidence; Analysis 1.1; Figure 2; Summary of findings 1). This corresponds to 750 deaths per 1000 participants with chemotherapy and 11 fewer (45 fewer to 26 more) deaths per 1000 participants with immunotherapy at 36 months. We downgraded the certainty of evidence one level for study limitations due to overall bias. For an analysis of absolute effect estimates, we used data from Powles 2021, which provides the most representative control event rate.
- Health-related quality of life

- Immunotherapy probably has little to no effect on health-related quality of life in the first-line therapy setting, when measured using the FACT-BL questionnaire and an MCID of at least 6 points (MD 4.10, 3.83 to 4.37; 1 study, 393 participants; moderate-certainty evidence; Analysis 1.2; Figure 3; Summary of findings 1). Using this instrument, a higher score represents a better health-related quality of life (scale from 0 to 156). We downgraded the certainty of evidence one level for study limitations due to overall bias. To estimate the MCID, we used data from Gopalakrishna 2017, which suggests that a difference of 6 to 8 points is clinically important.

- Adverse events grade 3 to 5
  - Immunotherapy probably reduces adverse events grade 3 to 5 in participants undergoing first-line therapy (RR 0.47, 95% CI 0.29 to 0.75; IY = 97%; 3 studies, 2046 participants; moderate certainty evidence; Analysis 1.3; Figure 4; Summary of findings 1). This corresponds to 908 grade 3 to 5 adverse events per 1000 participants with chemotherapy and 481 fewer (644 fewer to 227 fewer) grade 3 to 5 adverse events per 1000 participants with immunotherapy at 12 months' follow-up. We downgraded the certainty of evidence one level for study limitations due to overall bias. Although the I2 of 97% indicates substantial heterogeneity, this is probably because of differences in the size of the effect and not inconsistency in the direction of the effect (i.e. all three studies found in favor of immunotherapy but to differing degrees). For analysis of absolute effect size estimates, we used data from Galsky 2020, which provides the most representative control event rate. The most frequently reported grade 3 to 5 adverse events with immunotherapy were urinary tract infections (23 events), anemia (16 events) and asthenia (10 events). For participants receiving chemotherapy, they were anemia (148 events), neutropenia (117 events) and neutrophil count decrease (96 events).

- Time to death from bladder cancer
  - No studies reported time to death from bladder cancer.

- Discontinuation due to adverse events
  - Immunotherapy may reduce discontinuations due to adverse effects (RR 0.47, 95% CI 0.20 to 1.10; IY = 94%; 3 studies, 2046 participants; low-certainty evidence; Analysis 1.5; Figure 6; Summary of findings 1). This corresponds to 338 discontinuations per 1000 participants with chemotherapy and 179 fewer (271 fewer to 34 more) discontinuations per 1000 participants with immunotherapy after 12 months. We downgraded the certainty of evidence two levels for study limitations due to overall bias and imprecision. For the analysis of absolute effects, we used data from Galsky 2020.

Immunotherapeutic agent: atezolizumab versus pembrolizumab versus durvalumab

- Time to death from any cause
  - We performed subgroup analyses for time to death from any cause for participants in the first-line therapy setting under immunotherapy for atezolizumab versus pembrolizumab versus durvalumab (Analysis 1.6). Of 2068 included participants, 719 received atezolizumab, 659 received pembrolizumab and 690 received durvalumab. Our analysis found no evidence to suggest a subgroup effect (atezolizumab versus pembrolizumab versus durvalumab; test for subgroup diKerences: P = 0.74).

- Health-related quality of life
  - We could not conduct the planned subgroup analyses due to a lack of relevant data in the included studies.

- Adverse events grade 3 to 5

- We performed subgroup analyses for grade 3 to 5 adverse events for participants in the first-line therapy setting for immunotherapy with atezolizumab versus pembrolizumab versus durvalumab (Analysis 1.7). Of 2046 included participants, 744 received atezolizumab, 644 received pembrolizumab and 658 received durvalumab. Our analysis suggested a possible subgroup effect favoring durvalumab over atezolizumab over pembrolizumab (test for subgroup diKerences: P < 0.00001).

Anmerkung/Fazit der Autoren

In a first-line therapy setting, immunotherapy probably has little to no effect on the risk of death from any cause (moderate-certainty evidence). It probably has little to no effect on health-related quality of life (moderate-certainty evidence). Immunotherapy probably reduces grade 3 to 5 adverse events in participants undergoing first-line therapy (moderate-certainty evidence).

Based on recent randomized controlled trials for the treatment of advanced or metastatic urothelial carcinoma in the first-line therapy setting, immunotherapy, compared to chemotherapy, probably has little to no effect on the risk of death from any cause over time (moderate-certainty evidence), but probably reduces serious adverse events (moderate-certainty evidence). In addition, immunotherapy probably increases the risk of disease progression over time (moderate-certainty evidence), but probably has little to no effect on the quality of life (moderate-certainty of evidence) and may reduce discontinuations due to adverse events (low-certainty evidence).

3.2 Systematische Reviews

Mamede I et al., 2024 [5].

Immunotherapy Plus Chemotherapy Versus Chemotherapy Alone as First-Line Treatment for Advanced Urothelial Cancer: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

Fragestellung

Our objective is to address this ambiguity by conducting a systematic review and meta-analysis of RCTs, specifically evaluating the efficacy of ICIs combined with platinum-based CTX versus CTX alone in patients with previously untreated advanced urothelial cancer.

Methodik

Population:

- patients diagnosed with advanced urothelial cancer
- first-line treatment

Intervention/Komparator:

- Immunotherapy Plus Chemotherapy Versus Chemotherapy Alone

Endpunkte:

- Primary endpoints were
  (1) overall survival (OS) and
  (2) progression-free survival (PFS).
- Secondary endpoints were defined as
  (1) objective response rate (ORR),
  (2) safety

Recherche/Suchzeitraum:

- Embase, Medline (PubMed), and the Cochrane Central Register of Controlled Trials
- -01-2024

Qualitätsbewertung der Studien:

- Cochrane Collaboration Tool (RoB-2)

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTS (4 Reports)

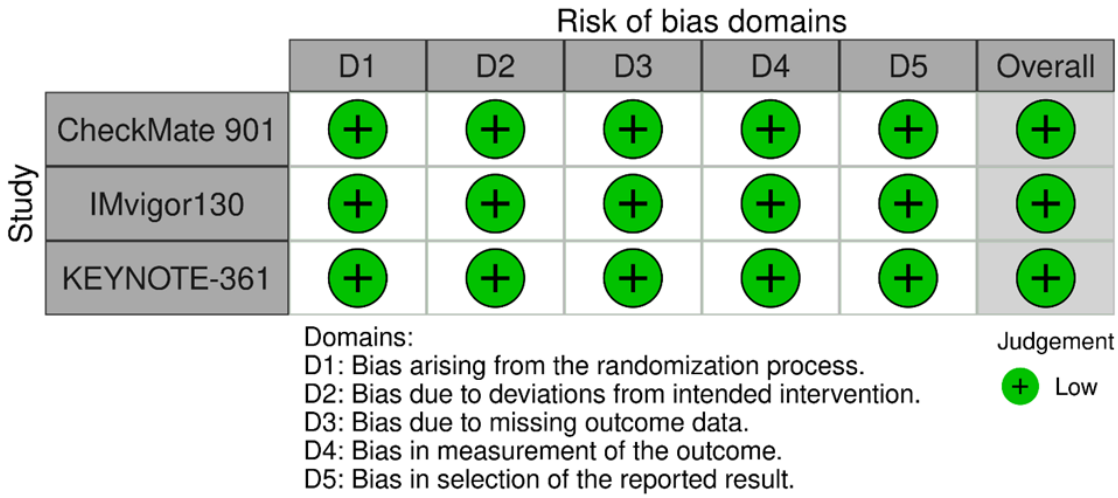
Charakteristika der Population/Studien:

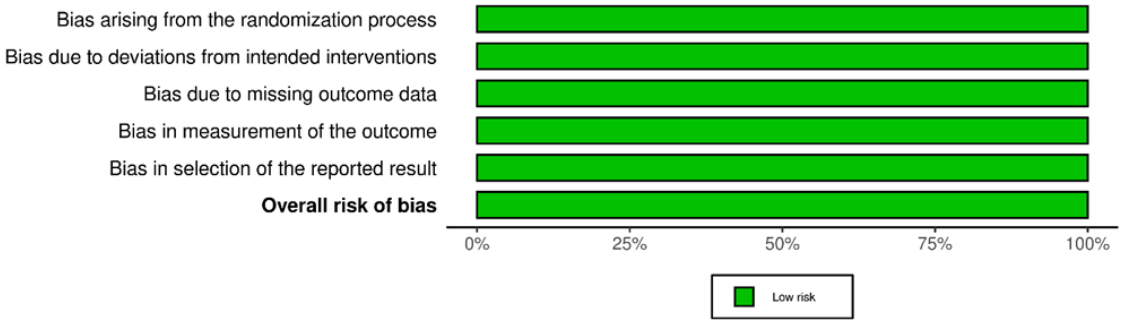
Table 1 Baseline Characteristics of Included Trials

Study	ICI	Patients ICI/CT	Age*, y ICI/CT	Male, % ICI/CT	PD-L1 ≥1, % ICI/CT	ECOG 2, % ICI/CT	Cisplatin, % ICI/CT	Follow-up*, mo
CheckMate 901[10]	Nivolumab	304/304	65/65	78/77	37/36	1/0	100/100	33.6
IMvigor130[6,19]	Atezolizumab	451/400	60/67	75/75	67/68	13/10	30/37	11.8
KEYNOTE-361[7]	Pembrolizumab	351/352	69/69	78/74	NA	7/6	44/44	31.7

ECOG = Eastern Cooperative Oncology Group Performance Scale Status; ICI = immune checkpoint inhibitors; PD-L1 = programmed cell death 1 protein ligand.
* Mean or median.

Qualität der Studien:





Studienergebnisse:

Figure 2 Overall survival comparison between treatment groups. Immuno-chemotherapy is associated with improved survival compared to chemotherapy alone ($P < .001$). CI = confidence interval; CTX = chemotherapy; ICI = immune checkpoint inhibitors; IV = inverse variance.

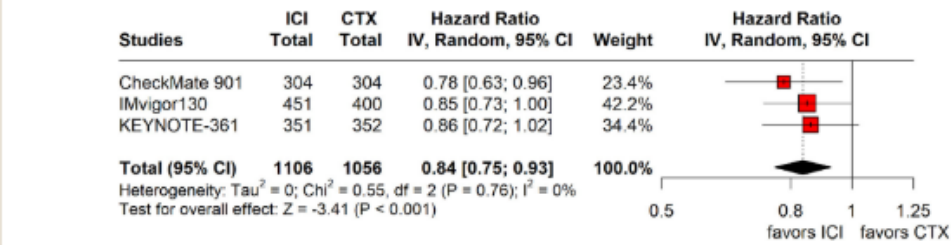
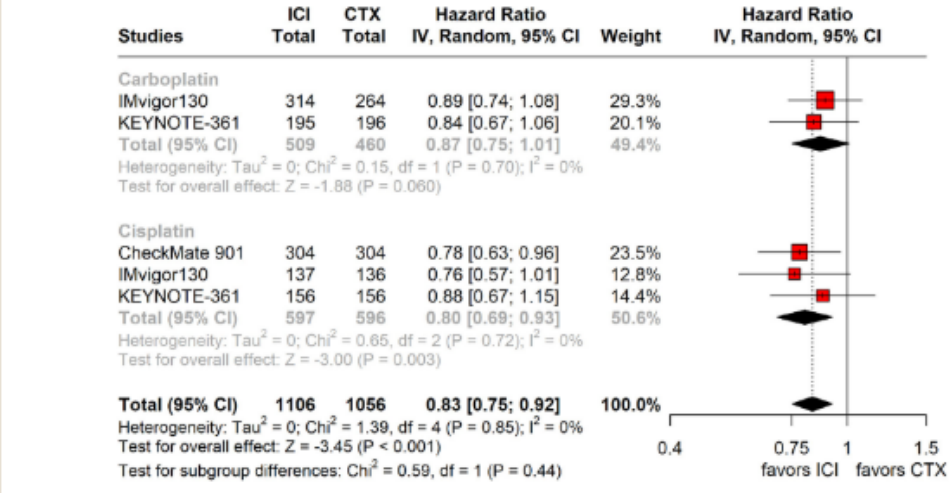


Figure 3 Overall survival in platinum-chemotherapy subgroups. No subgroup differences were found (*P*-interaction = .44). CI = confidence interval; CTX = chemotherapy; ICI = immune checkpoint inhibitors; IV = inverse variance.



Anmerkung/Fazit der Autoren

Our findings indicate that this integrated approach offers substantial improvements in both overall and progression-free survival for patients with advanced urothelial cancer, compared to platinum based chemotherapy alone. Furthermore, the combination therapy is associated with a superior objective response rate, but with an increased the 3–5 grade immune-related toxicity. These results provide robust support for considering the use of ICI in conjunction with chemotherapy as an initial treatment option for patients with advanced urothelial cancer. As our findings align with emerging evidence, this combined therapeutic strategy approach shows potential in enhancing outcomes, presenting the ICI-CTX combination as a preferable alternative for cisplatin eligible patients unable to receive EV-P combination.

Chen HL et al., 2021 [1].

Immune Checkpoints Inhibitors and Chemotherapy as First-Line Treatment for Metastatic Urothelial Carcinoma: A Network Meta-Analysis of Randomized Phase III Clinical Trials

Fragestellung

Hence, we conducted a network metaanalysis (NMA) to investigate and compare the treatment response and toxicity of PD-1/L1 inhibitors versus chemotherapy as a first-line treatment for patients with mUC.

Methodik

Population:

- adult with advanced or metastatic TCC or UC
- treatment-naïve patients

Intervention/Komparator:

- immunotherapy and the standard treatment arm with chemotherapy

Endpunkte:

- Our primary outcome was the treatment efficacy, which was evaluated by overall survival (OS), progression of free survival (PFS), as well as the objective response rate (ORR).
- Our secondary outcome was the safety profile focusing on grade 3–5 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE)

Recherche/Suchzeitraum:

- -14.10.2020

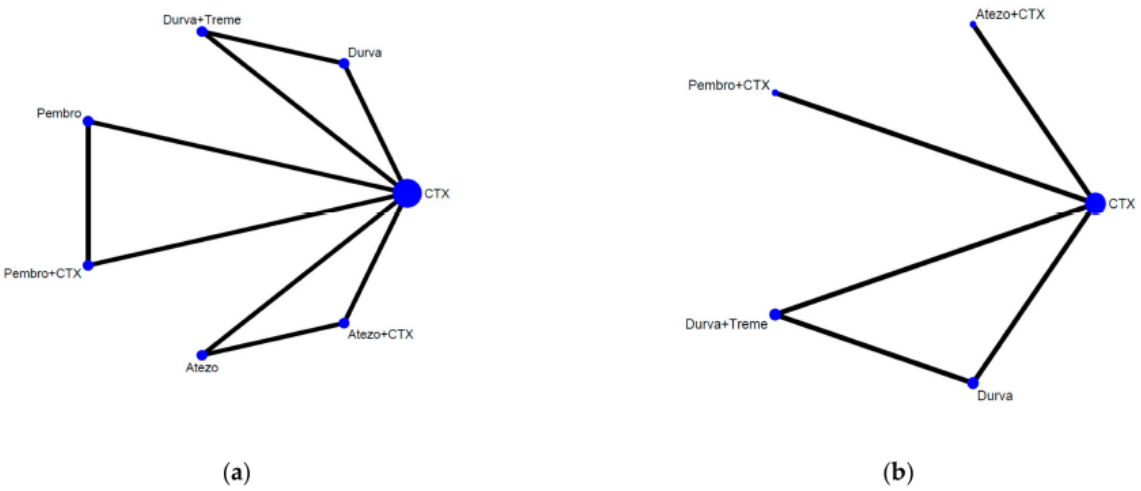
Qualitätsbewertung der Studien:

- risk of bias (ROB) tool
- Based on Table 1 and Figure 2, the network plot showed that each of the three loops is formed by a three-arm trial, and therefore, for any direct treatment comparison, its direct and indirect evidence comes from the same trial. Consequently, by definition, the evidence is always consistent.

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 published studies retrieved from three completed RCTs



(a) (b)

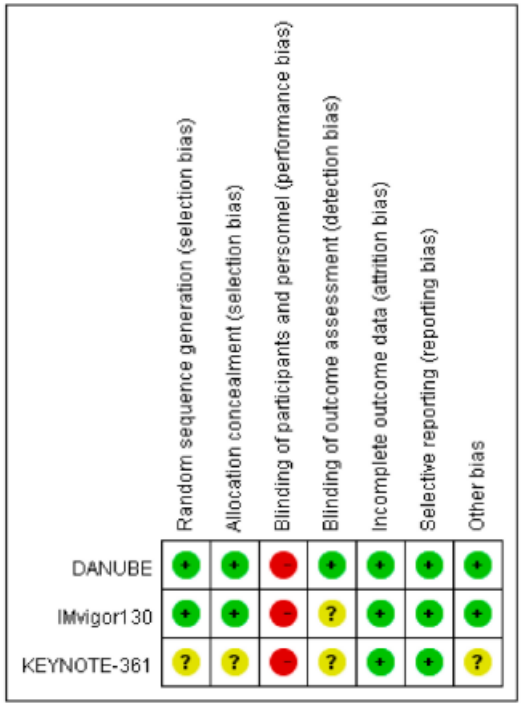
Figure 2. Network constructions for comparison in overall survival (OS), progression of free survival (PFS), objective response rate (ORR), and grade 3–5 adverse events (AEs). (**a**) Network constructions for comparison in OS (hazard ratio (HR)), ORR, grade 3-5 AEs. (**b**) Network constructions for comparison in PFS (HR).

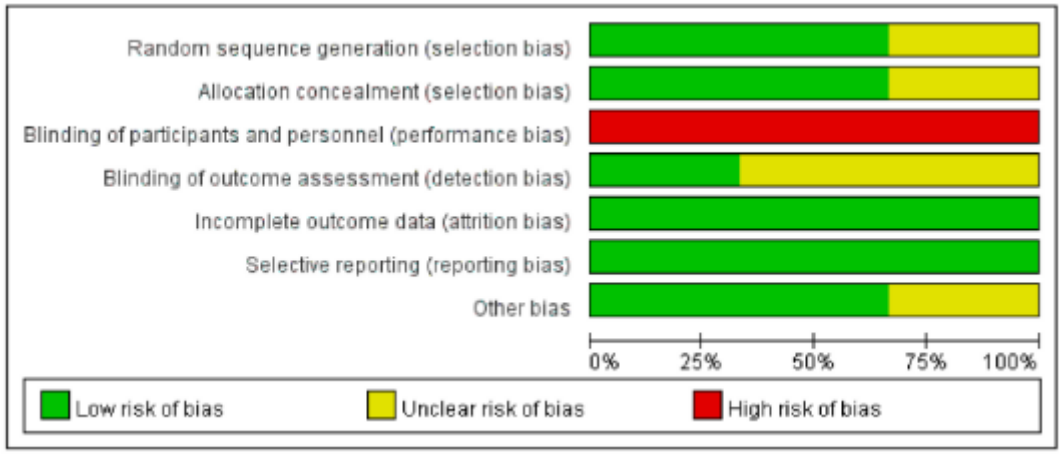
Charakteristika der Population/Studien:

Table 1. Characteristics of the included studies.

Trial Name	Year	NCT Number	Phase	ICI-Based Treatment	ICI Category	Design	Stage	Median Age	Males (%)	Site of Metastatic Disease (%)	Treatment Arm (Patient Number)
IMvigor130	2020	NCT02807636	3	atezolizumab	PD-L1 inhibitors	three arms open-label	advanced or metastatic	67–69	75–77	Lymph node only (17.89%) Visceral metastases (79.96%)	1. atezolizumab (360) 2. atezolizumab + platinum-based CTX (451) 3. platinum-based CTX (400)
DANUBE	2020	NCT02516241	3	durvalumab tremelimumab	PD-L1 inhibitors CTLA4 inhibitors	three arms open-label	advanced or metastatic	67–68	72–80	Lymph node only (20.45%) Visceral metastases (79.36%)	1. durvalumab (346) 2. durvalumab + tremelimumab (342) 3. platinum-based CTX (344)
KEYNOTE-361	2020	NCT02853305	3	pembrolizumab	PD-1 inhibitors	three arms open-label	advanced or metastatic	68–69	74.3–77.5	Lymph node only (23.66%) Visceral metastases (74.26%)	1. pembrolizumab (307) 2. pembrolizumab + platinum-based CTX (351) 3. platinum-based CTX (352)

Qualität der Studien:





Studienergebnisse:

- Overall Survival
  - Although no superior effects were indicated, combination therapy presented lower HRs compared with CTX alone (HR = 0.83, 95% CI = 0.69–1.00 for Atezo plus CTX, HR = 0.86, 95% CI = 0.72–1.03 for Pembro plus CTX, HR = 0.85, 95% CI = 0.72–1.00 for Durva plus Treme). In terms of monotherapy, the survival benefit of single ICI was non-inferiority to CTX alone (HR = 1.02, 95% CI = 0.83–1.25 for Atezo, HR = 0.92, 95% CI = 0.77–1.10 for Pembro, HR = 0.99, 95% CI = 0.83–1.18 for Durva). In addition, no significant differences were presented among combination therapy (HR = 1.04, 95% CI = 0.80–1.34 for Pembro plus CTX vs. Atezo plus CTX, HR = 1.02, 95% CI = 0.80–1.31 for Durva plus Treme vs. Atezo plus CTX, HR = 0.99, 95% CI = 0.77–1.26 for Durva plus Treme vs. Pembro plus CTX) and similar effects were presented among monotherapy (HR = 0.93, 95% CI = 0.72–1.19 for Pembro vs. Durva, HR = 1.03, 95% CI = 0.79–1.35 for Atezo vs. Durva, HR = 1.11, 95% CI = 0.84–1.46 for Atezo vs. Pembro). Regarding the SUCRA ranking (Figure 4a), the probability of Atezo plus CTX was associated with the best ranking for OS (highest SUCRA and Prbest value, SUCRA = 80.2%, Prbest = 38.6%, Figure A2), followed by Durva plus Treme (SUCRA = 75.6%), Pembro plus CTX (SUCRA = 70.6%), Pembro (SUCRA = 50.8%), Durva (SUCRA = 29.7%), CTX alone (SUCRA = 22.0%,) and Atezo (SUCRA = 21.7%).
- 2.3.4. Grade 3–5 Adverse Events
  - We found no significant differences in the risk of grade 3–5 adverse events between ICIs plus CTX and CTX (risk ratio = 1.00, 95% CI = 0.96–1.05 for Atezo plus CTX, risk ratio = 1.07, 95% CI = 1.00–1.14 for Pembro plus CTX). Additionally, a lower risk was observed among Durva plus Treme users compared with CTX (risk ratio = 0.89, 95% CI = 0.81–0.97 for Durva plus Treme). In terms of monotherapy, patients with ICIs presented better safety profile than CTX alone (risk ratio = 0.55, 95% CI = 0.49–0.61 for Atezo, risk ratio = 0.77, 95% CI = 0.70–0.85 for Pembro and risk ratio = 0.75, 95% CI = 0.67–0.84 for Durva) and patients with Atezo presented a significantly lower risk than Pembro and Durva (risk ratio = 0.71 95% CI = 0.62–0.83 for Pembro, risk ratio = 0.73, 95% CI = 0.63–0.85 for Durva). Based on the SUCRA value, that larger SUCRA value indicated the lower risk of adverse events. Atezo had the best safety profile (SUCRA = 100%, Prbest = 100% Figures 4d and A2), followed by Durva (SUCRA = 77.3%), Pembro (SUCRA = 72.2%), Durva plus Treme (SUCRA = 50.2%), CTX (SUCRA = 25.3%), Atezo + CTX (SUCRA = 23.9%), and Pembro + CTX (SUCRA = 1.0%).

Anmerkung/Fazit der Autoren

From this NMA focusing on the first-line treatment of mUC patients, combination therapy (either ICIs plus CTX or ICIs plus ICIs) had a higher priority in terms of OS upon the ranking analysis. Concerning monotherapy, ICIs are not inferior to CTX in terms of OS. The benefit of combination therapy is presented regardless of gender and age upon the subgroup analysis. In view of the adverse effect, ICIs are very tolerable, and combination therapy did not lead to a higher incidence of grade 3–5 AEs when compared with CTX.

Kommentare zum Review

Die SR von Martini [7], Mao [6], Liao [3] und Huang [2] haben sich mit der gleichen Fragestellung beschäftigt und analysierten die gleichen Studien.

3.3 Leitlinien

Witjes JA et al., 2023 [9].

European Association of Urology (EAU)

EAU guidelines on muscle-invasive and metastatic bladder cancer

Zielsetzung/Fragestellung

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) have prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse werden nicht beschrieben; ein externes Begutachtungsverfahren / Review wird dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- -05.2023
- MEDLINE, Embase, Cochrane Libraries

LoE

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

GoR

The strength rating forms draw on the guiding principles of the GRADE methodology but do not purport to be GRADE. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are grade according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);

3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Zusammenfassung der Empfehlungen

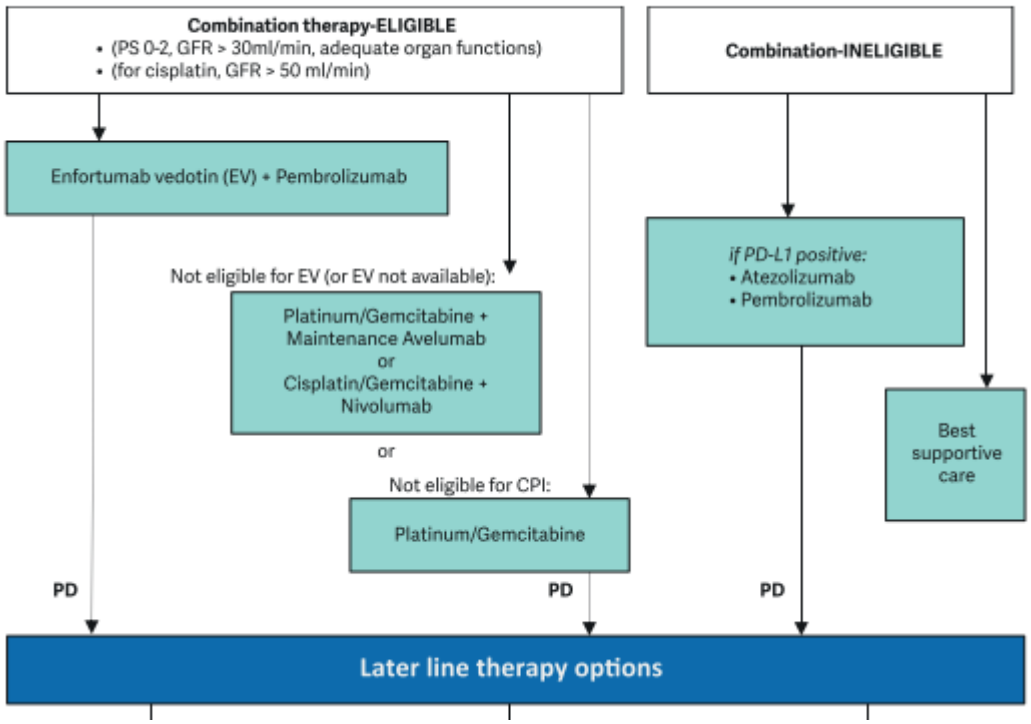
7.7.9 ***Summary of evidence and recommendations for metastatic disease***

Summary of evidence	LE
Enfortumab vedotin in combination with pembrolizumab in the first-line setting demonstrated significant survival benefit as compared to chemotherapy.	1
The combination of cisplatin and gemcitabine plus Nivolumab in the first-line setting demonstrated significant survival benefit as compared to chemotherapy alone.	1b
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term DFS reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
There is no defined standard therapy for platinum chemotherapy-unfit patients with advanced or metastatic UC.	2b
Post-chemotherapy surgery after partial or complete response may contribute to long-term DFS in highly selected patients.	3
Zoledronic acid and denosumab have been approved for supportive treatment in case of bone metastases of all cancer types including UC, as they reduce and delay skeletal related events.	1b

PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-L1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b
PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-L1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-L1 status).	1b
The combination of chemotherapy plus pembrolizumab or atezolizumab and the combination of durvalumab and tremelimumab have not demonstrated OS survival benefit compared to platinum-based chemotherapy alone.	1b
Switch maintenance with the PD-L1 inhibitor avelumab has demonstrated significant OS benefit in patients achieving at least stable disease on first-line platinum-based chemotherapy.	1b

Recommendations	**Strength rating**
First-line treatment if eligible for combination therapy	
Use antibody drug conjugate enfortumab vedotin (EV) in combination with checkpoint inhibitor (CPI) pembrolizumab.	Strong
If contraindications for EV or EV not available: Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine) followed by maintenance treatment with CPI avelumab in patients with at least stable disease on chemotherapy.	Strong
If contraindications for EV (or EV not available) and cisplatin-eligible: Consider cisplatin/gemcitabine in combination with CPI nivolumab.	Strong
If contraindications for checkpoint inhibitor therapy: Use platinum-containing combination chemotherapy (Cisplatin or carboplatin plus gemcitabine).	Strong
First-line treatment if not eligible for combination therapy	
Consider single agent CPI pembrolizumab or atezolizumab in case of high PD-1 expression. (for definitions see text).	Weak

Figure 7.2: Flow chart for the management of metastatic urothelial cancer*



Masson-Lecomte P et al., 2024 [8].

European Association of Urology (EAU)

EAU guidelines on upper urinary tract urothelial carcinoma

Zielsetzung/Fragestellung

This overview represents the updated European Association of Urology (EAU) Guidelines for the management of upper urinary tract urothelial carcinoma (UTUC).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse werden nicht beschrieben; ein externes Begutachtungsverfahren / Review wird dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- -01.05.2023
- Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews

LoE

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

GoR

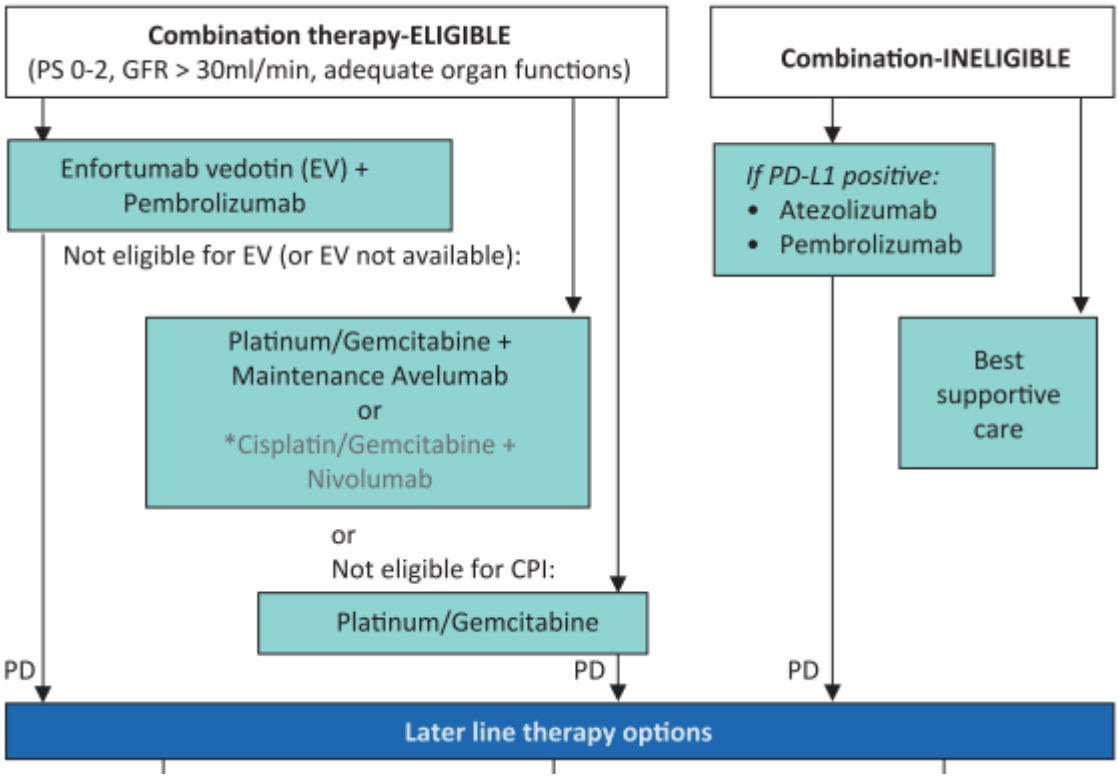
The strength rating forms draw on the guiding principles of the GRADE methodology but do not purport to be GRADE. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are grade according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Zusammenfassung der Empfehlungen

Figure 7.3 Flowchart for the management of metastatic upper tract urothelial carcinoma



7.3.3 ***Summary of evidence and recommendations for the treatment of metastatic UTUC***

Summary of evidence	LE
Enfortmab vedotin + Pembrolizumab offers an overall survival benefit compared to gemcitabine-cisplatin in the 1st line setting.	1b
Cisplatin-based combination chemotherapy can improve median survival.	2
Cisplatin-containing combination chemotherapy is the standard of care in advanced or metastatic patients fit enough to tolerate cisplatin and who are ineligible for Enfortumab + Pembrolizumab.	1b
Cisplatin-containing combination chemotherapy in combination with nivolumab offers a survival advantage compared with chemotherapy alone in the 1st line setting.	1b

Carboplatin-based combination chemotherapy offers a survival benefit in cisplatin unfit patients.	1b
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus either cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab has been approved for patients who have experienced disease progression during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b
PD-1 inhibitor nivolumab has been approved for patients that have experienced disease progression during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial, but use of atezolizumab is restricted to PD-L1 positive patients.	2a
Erdafitinib was associated with improved overall survival in platinum-refractory patients with locally-advanced or metastatic UC and FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 fusions).	1b
Enfortumab vedotin was associated with OS benefit in patients who had previously received platinum-containing chemotherapy and experienced disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	1b
Palliative nephroureterectomy can improve quality of life by controlling symptomatic disease.	3
RNU can confer a survival benefit in highly selected patients with metastatic UC e.g., after response to platinum-based combination chemotherapy with limited metastatic burden.	4

Recommendations	Strength rating
Offer Enfortumab vedotin in combination with pembrolizumab as first line treatment to patients with advanced/metastatic disease.	Strong
First-line treatment for platinum-eligible patients who are unsuitable/ineligible for Enfortumab + Pembrolizumab	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin based chemotherapy with gemcitabine-cisplatin + nivolumab in cisplatin eligible patients.	Weak
Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients.	Strong
Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
Offer maintenance avelumab to patients who did not have disease progression after 4 to 6 cycles of platinum-based combination chemotherapy.	Strong
First-line treatment in patients ineligible for any combination therapy	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
Later lines of treatment	
Offer platinum based combination chemotherapy as second line treatment of choice if not received in the first line setting.	Strong
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease who did not receive maintenance avelumab.	Strong
Offer enfortumab vedotin to patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	Strong

Test UTUC patients for FGFR alterations (FGFR2/3 mutations or FGFR3 fusions) prior to erdafitinib treatment.	Strong
Offer erdafitinib as an alternative subsequent-line therapy to patients: • previously treated with platinum-containing chemotherapy; • who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor; • who harbour FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 fusions).	Strong
Only offer vinflunine to patients with metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-line treatment.	Strong
Offer nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally-advanced tumours.	Weak

DNA = deoxyribonucleic acid; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 08 of 12, August 2024) am 13.08.2024

#	Suchfrage
1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
2	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
3	(bladder OR urotheli* OR transitional):ti,ab,kw
4	(tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR neoplas* OR cancer*):ti,ab,kw
5	#1 OR #2 OR (#3 AND #4)
6	#5 with Cochrane Library publication date from Aug 2019 to present

Systematic Reviews in PubMed am 13.08.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"urinary bladder neoplasms/therapy"[mh]
2	"carcinoma, transitional cell/therapy"[mh]
3	bladder[ti] OR urotheli*[ti] OR transitional[ti]
4	tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR cancer*[ti]
5	urologic*[ti] OR urinary[ti] OR genitourinary[ti] OR urogenital[ti]
6	bladder[tiab] OR urotheli*[tiab] OR transitional[tiab]
7	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR cancer*[tiab]
8	treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab] OR chemotherap*[tiab] OR immunotherap*[tiab] OR radiotherap*[tiab]
9	#3 AND #4 AND #8
10	#5 AND #6 AND #7 AND #8
11	(#6 AND #7 AND #8) NOT medline[sb]
12	#1 OR #2 OR #9 OR #10 OR #11
13	(#12) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab]

#	Suchfrage
	OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
14	(#13) AND ("2019/08/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT "The Cochrane database of systematic reviews"[Journal]
16	(#15) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 13.08.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	urinary bladder neoplasms[mh]
2	carcinoma, transitional cell[mh]
3	bladder[ti] OR urotheli*[ti] OR transitional[ti]
4	tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR cancer*[ti]
5	#1 OR #2 OR (#3 AND #4)
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(#6) AND ("2019/08/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 14.08.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Chen HL, Chan VW, Tu YK, Chan EO, Chang HM, Juan YS, et al.** Immune checkpoints inhibitors and chemotherapy as first-line treatment for metastatic urothelial carcinoma: a network meta-analysis of randomized phase III clinical trials. Cancers (Basel) 2021;13(6):1484.
2. **Huang G, Xiong H, Li S, Zhu Y, Liu H.** The efficacy of immune checkpoint inhibitors therapy versus chemotherapy in the treatment of advanced and metastatic urothelial carcinoma: a meta-analysis. J Cancer Res Clin Oncol 2024;150(1):5.
3. **Liao PF, Wang PY, Peng TR.** Efficacy and safety of programmed death-1/programmed death-ligand 1 inhibitor for metastatic urothelial carcinoma: a systematic review and meta-analysis. Curr Oncol 2023;30(11):9940-9952.
4. **Maisch P, Hwang EC, Kim K, Narayan VM, Bakker C, Kunath F, et al.** Immunotherapy for advanced or metastatic urothelial carcinoma. Cochrane Database of Systematic Reviews [online]. 2023(10):Cd013774. URL: http://dx.doi.org/10.1002/14651858.CD013774.pub2.
5. **Mamede I, Escalante-Romero L, Celso DSG, Reis PCA, Dacoregio MI, Alves AC, et al.** Immunotherapy plus chemotherapy versus chemotherapy alone as first-line treatment for advanced urothelial cancer: an updated systematic review and meta-analysis of randomized controlled trials. Clin Genitourin Cancer 2024;22(5):102154.
6. **Mao L, Yang M, Fan X, Li W, Huang X, He W, et al.** PD-1/L1 inhibitors can improve but not replace chemotherapy for advanced urothelial carcinoma: a systematic review and network meta-analysis. Cancer Innov 2023;2(3):191-202.
7. **Martini A, Raggi D, Fallara G, Nocera L, Schultz JG, Belladelli F, et al.** Immunotherapy versus chemotherapy as first-line treatment for advanced urothelial cancer: a systematic review and meta-analysis. Cancer Treat Rev 2022;104:102360.
8. **Masson-Lecomte A, Gontero P, Birtle A, Compérat E, Dominguez Escrig JL, Liedberg F, et al.** EAU guidelines on upper urinary tract urothelial carcinoma [online]. Arnhem (NED): European Association of Urology (EAU); 2024. [Zugriff: 14.08.2024]. URL: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Upper-Urinary-Tract-Urothelial-Carcinoma-2024.pdf.
9. **Witjes JA, Bruins HM, Carrion A, Cathomas R, Comperat E, Efstathiou JA, et al.** EAU guidelines on muscle-invasive and metastatic bladder cancer [online]. Arnhem (NED): European Association of Urology (EAU); 2024. [Zugriff: 14.08.2024]. URL: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Muscle-Invasive-and-Metastatic-Bladder-Cancer-2024.pdf.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO